Board Review 2008
Allergen Immunotherapy

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Disclosure: Harold S. Nelson MD

Below I have disclosed relevant commercial associations that might pose a conflict of interest: Date: 15 January, ,2008

- **Consultant Arrangements**:
- Genentech/Novartis — Dey Laboratories — Curalogic
- Dynavax Technologies — GlaxoSmithKline — Johnson & Johnson
- Schering-Plough (Integrated Therapeutics Group) — Abbott Laboratories
- MediciNova

- **Stock/Other Equity Ownership:** None

- **Patent Licensing Arrangements:** None

- **Grants/Research Support:**
- Novartis — Schering-Plough — TEVA — Behringer
- Sepracor — Altana — Genentech — Clinical Therapeutics
- Wyeth — GenTel — Abbott laboratories — Hoffman-laRoche
- GlaxoSmithKline

- **Employment:** None

- **Speakers' Bureau:**
- GlaxoSmithKline — AstraZeneca

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Present Status of Subcutaneous Immunotherapy (SCIT)

- Identified effective doses
- Plausible mechanism
- Demonstrated prevention of:
  a. New sensitization
  b. Progression from rhinitis to asthma
- Established duration
- Persistence of efficacy after stopping

But:

- Inconvenient
- Occurrence of systemic reactions.

Effective Doses in Double-Blind Studies (Major Allergen)

Allergen	Effective Doses	Less Effective Doses
Ragweed	4 to 24 µg Amb a 1	0.6 & 2.0 µg Amb a 1
D pt	3.25 to 12 µg Der p 1	0.7 µg Der p 1
D far	10 µg Der f 1	N.D
Timothy	15 & 20 µg Phl p 5	2.0 µg Phl p 5
Cat	11 to 17 µg Fel d 1	0.6 &3.0 µg Fel d 1
Dog	15 µg Can f 1	0.6 & 3.0 µg Can f 1
Birch	3.28 & 12 µg Bet v 1	N.D.
Alternaria	1.6 µg Alt a 1	N.D.

N.D. = Not determined

Immunotherapy: Mechanisms

Allergen Immunotherapy: Evidence for Relevant Effects on Bronchial Responses

- Decreased early response to inhalation of allergen (Bousquet, grass, house dust mite)
- Decreased late bronchial response to allergen (Van Bever, house dust mite)
- Decreased non-specific response to histamine (Hedlin, cat)

Allergen Immunotherapy: Evidence for Relevant Effects on Effector Cells of Allergic Inflammation

- Decreased seasonal rise in BALF eosinophils (Rak, birch)
- Decreased nasal metachromatic cells (Otsuka,house dust)
- Decreased cutaneous mast cells (Durham, grass)
- Decreased seasonal rise in nasal basophils and eosinophils.(Wilson, grass)

Immunologic Response to Allergen Immunotherapy

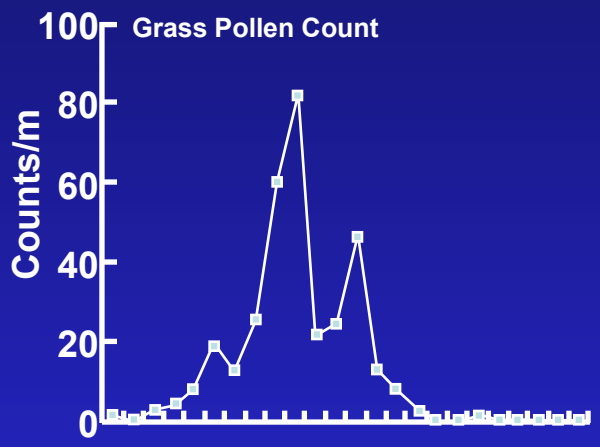
- Antibody Parameters
  - Rise in specific IgG (blocking antibody)
  - Initial rise then gradual fall in specific IgE
- T-lymphocyte parameters
  - Decreased proliferation and expression of Th2 cytokines in antigen stimulated lymphocytes
  - Increased expression of Th1 cytokines in allergen stimulated lymphocytes.
  - Increase in CD4+CD25+ regulatory t-lymphocytes secreting IL-10 & TGF-b

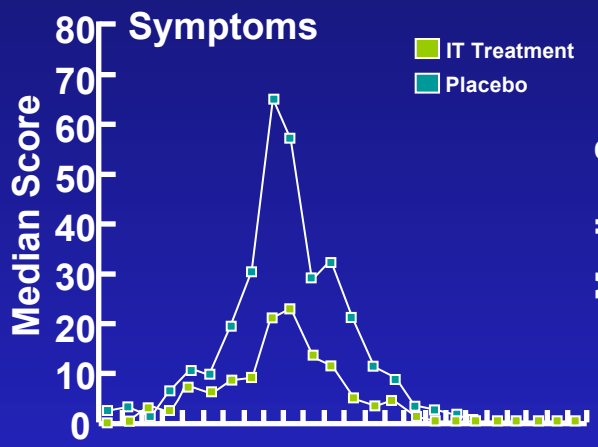
Increases in IL-12 mRNA^{+} Accompany Inhibition of Allergen Late Skin Test Responses after Successful Grass Pollen Immunotherapy

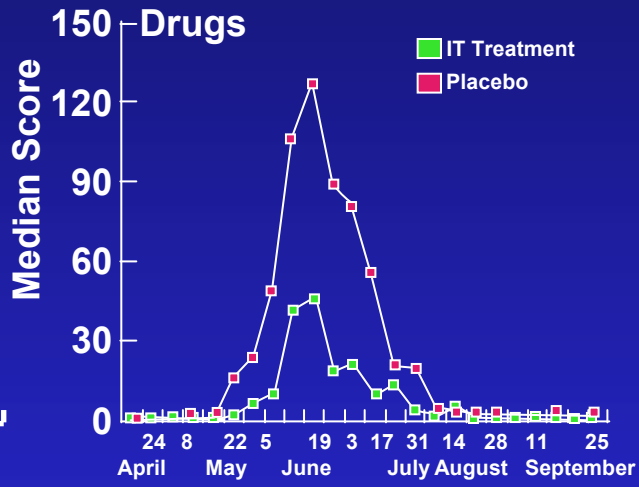
QA Hamid,et al.J Allergy Clin Immunol 1997;99:254-60

10 subjects who had received 4 years of grass pollen immunotherapy and 10 allergic controls had skin biopsies 24 hours after injection of grass pollen extract.

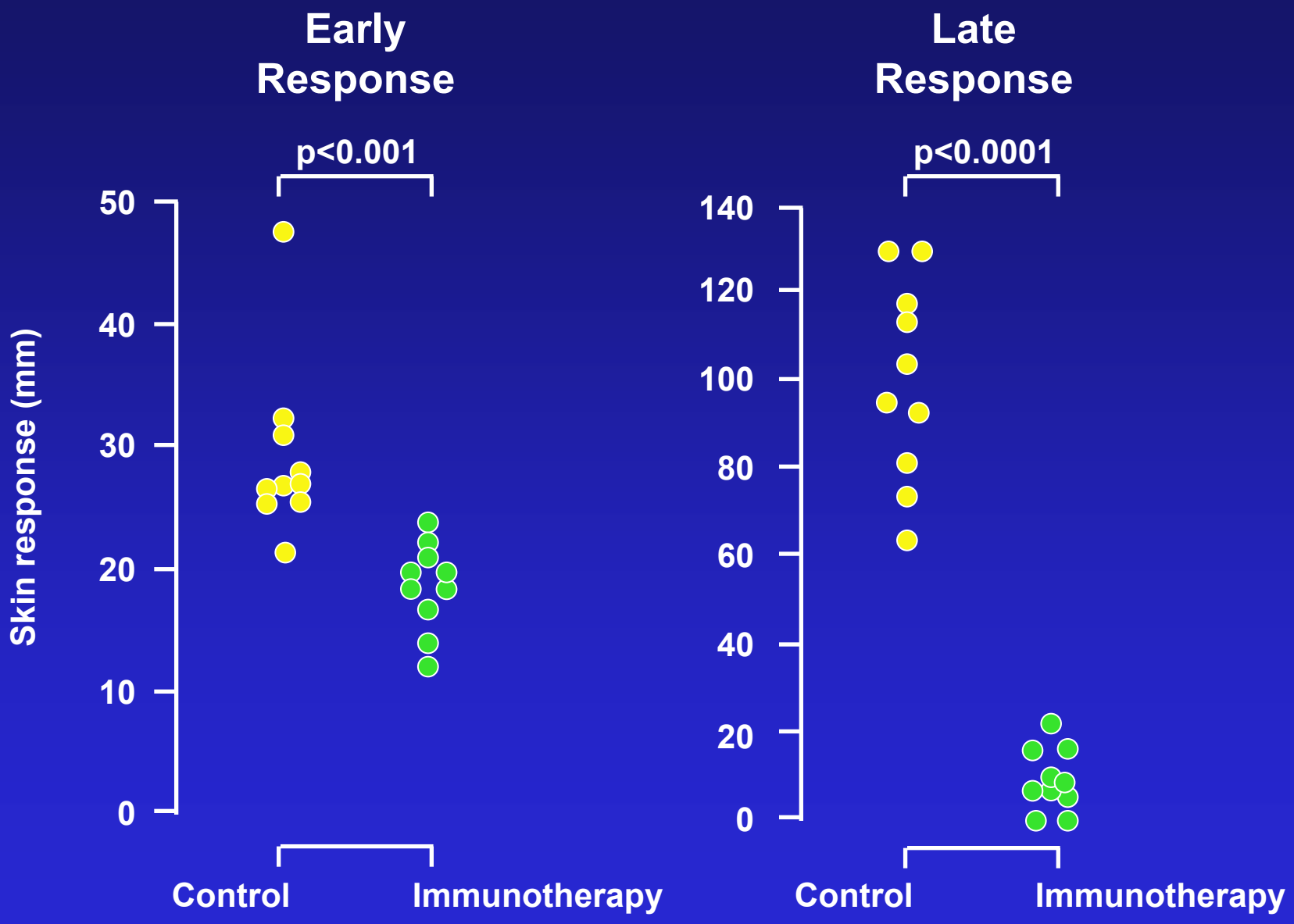
Reduction in Rhinitis Symptoms and Medication from Immunotherapy







(Varney et al. BMJ. 1991;302:265-269.)

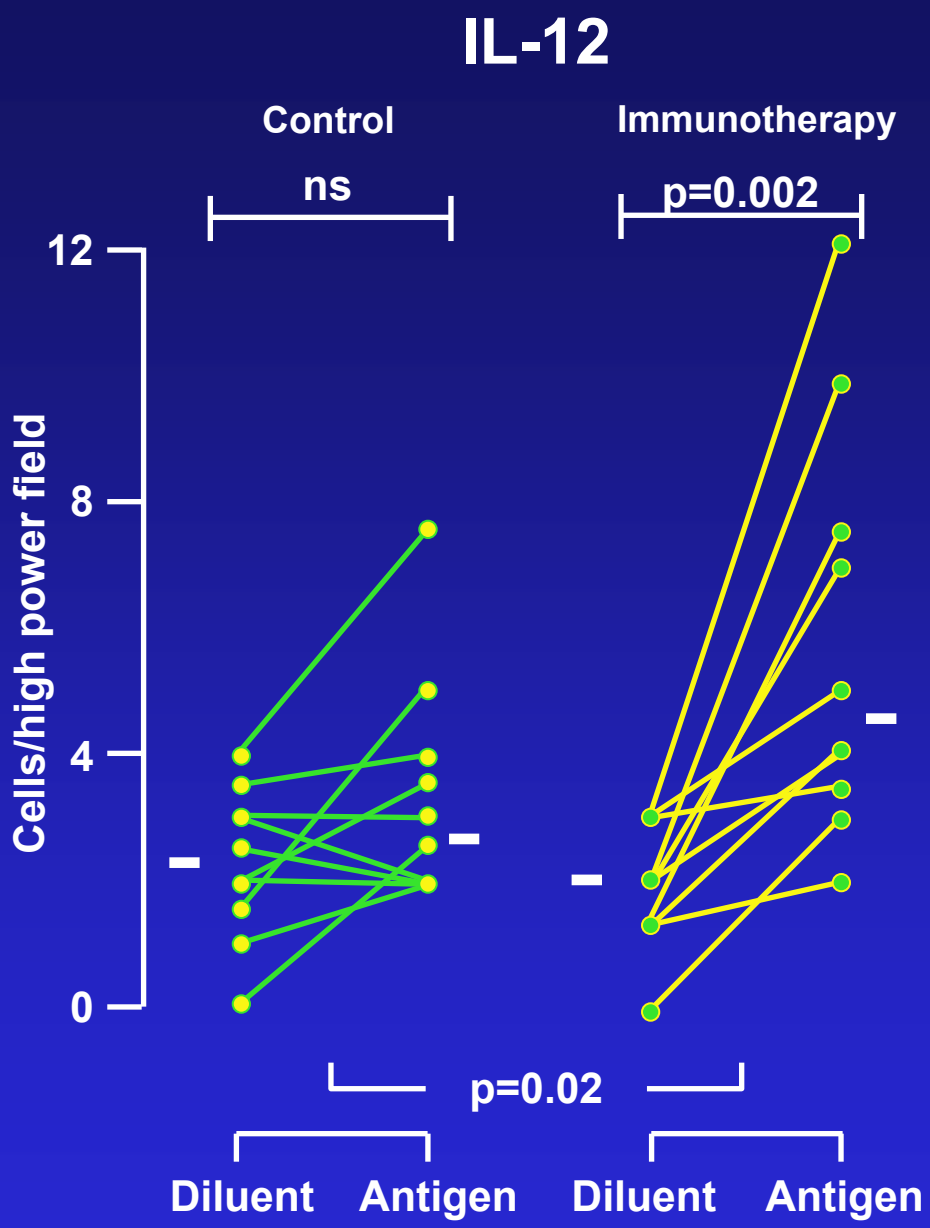


Hamid JACI 1997;99:254

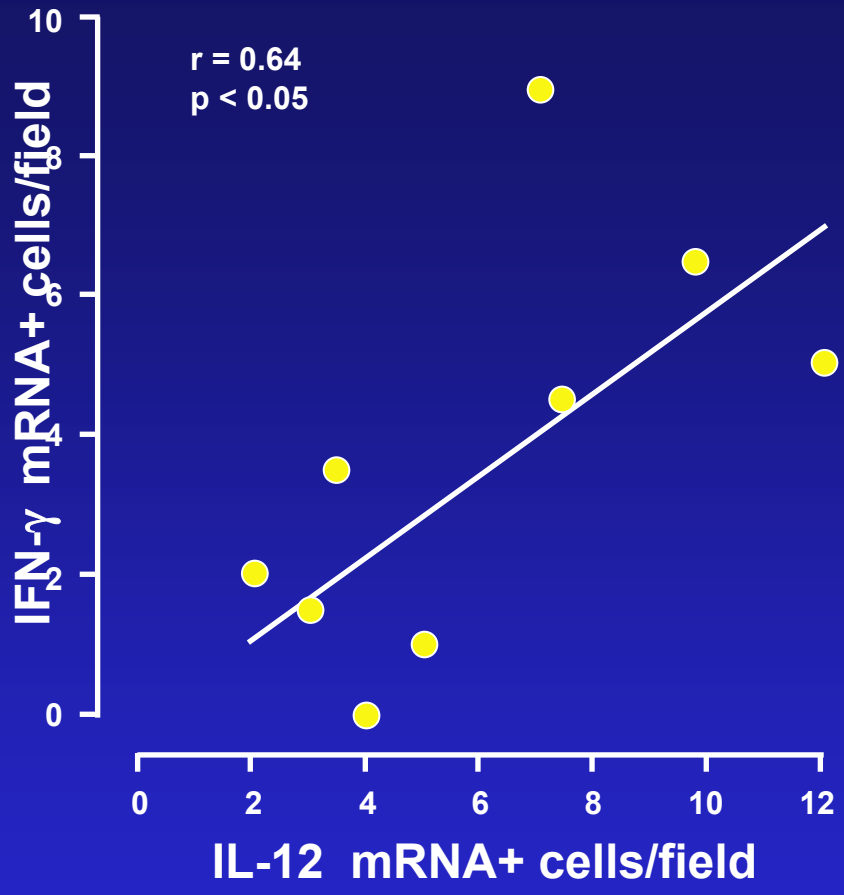
Late Skin Response to Allergen Following Successful Pollen Immunotherapy

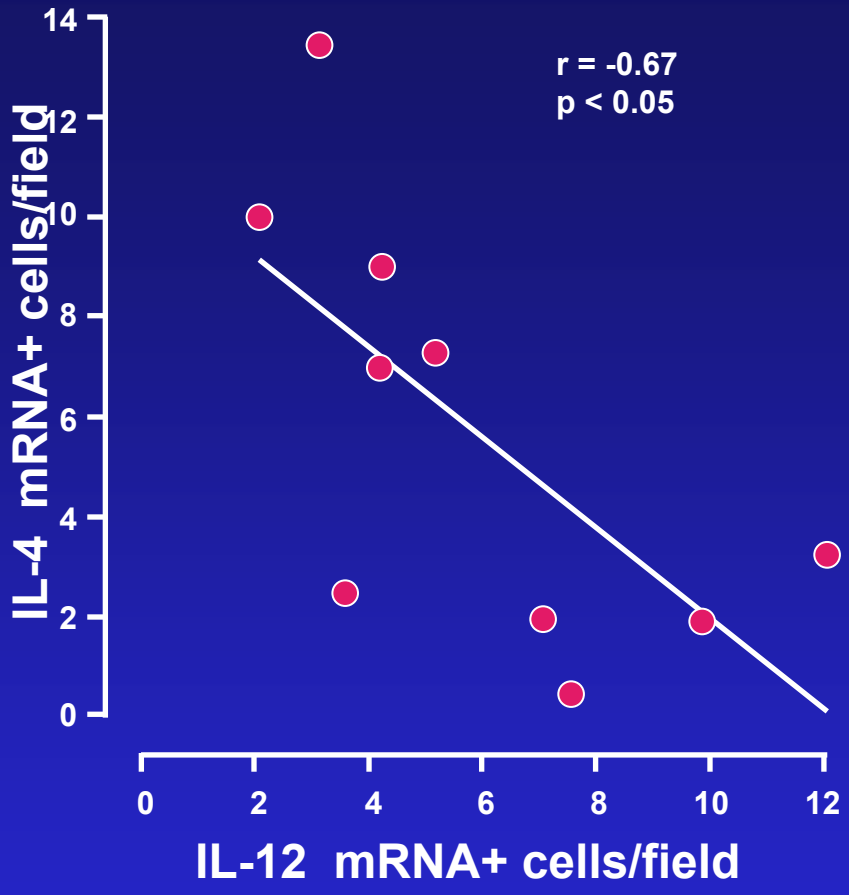
- At site of late cutaneous response:
  - Increased cells with mRNA for IL-12
  - Principal source of IL-12 tissue macrophages
- IL-12$^+$ cells correlated positively with IFN-χ^+ cells and inversely with IL-4$^+$ cells.

QA Hamid, et al JACI 1997



Hamid JACI 1997;99:254





Hamid et al, JACI 1997;99:254

IL-10 and TGF-b Cooperate in the Regulatory T Cell Response to Mucosal Allergens in Normal Immunity and Specific Immunotherapy

M Jutel, et al. Eur J Immunol 2003;33:1205-14

Examined the normal immunoregulatory mechanism and the immunologic basis of specific immunotherapy (SIT) to Der p 1 and Bet v 1

Regulatory T Cell Response

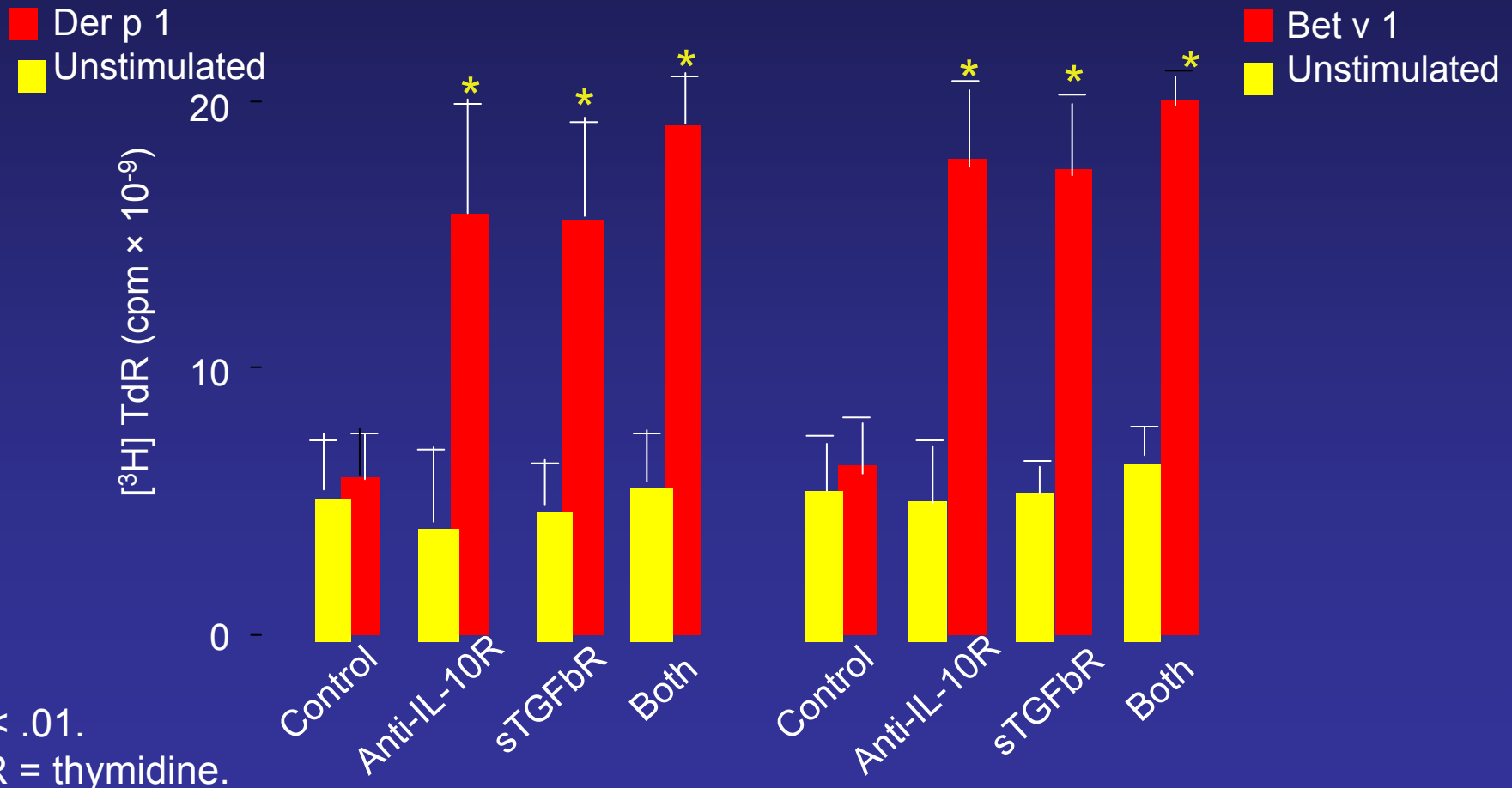
- In normal immunity to HDM and birch pollen an allergen-specific peripheral T cell suppression to Der p 1 and Bet v 1 was observed.
- This was characterized by:
  - suppressed proliferative T cell, (Th_1) INF-γ, and (Th_2) IL-5, IL-13 responses
  - increased IL-10 and TGF-β secretion by allergen-specific T cells.

Regulatory/Suppressor T Cell Response to Allergen Immunotherapy

- Immunotherapy to house dust mite extract induced antigen-specific suppressive activity in CD4+CD25+ T cells in allergic subjects.
- The regulatory/suppressor T cells secreted IL-10 and TGF-B
- These cytokines induce IgG4 and IgA and suppress IgE production by B cells.
- Mimics the healthy immune response to environmental allergens.

Jutel et al. Eur J Imm 2003;33:1205-14

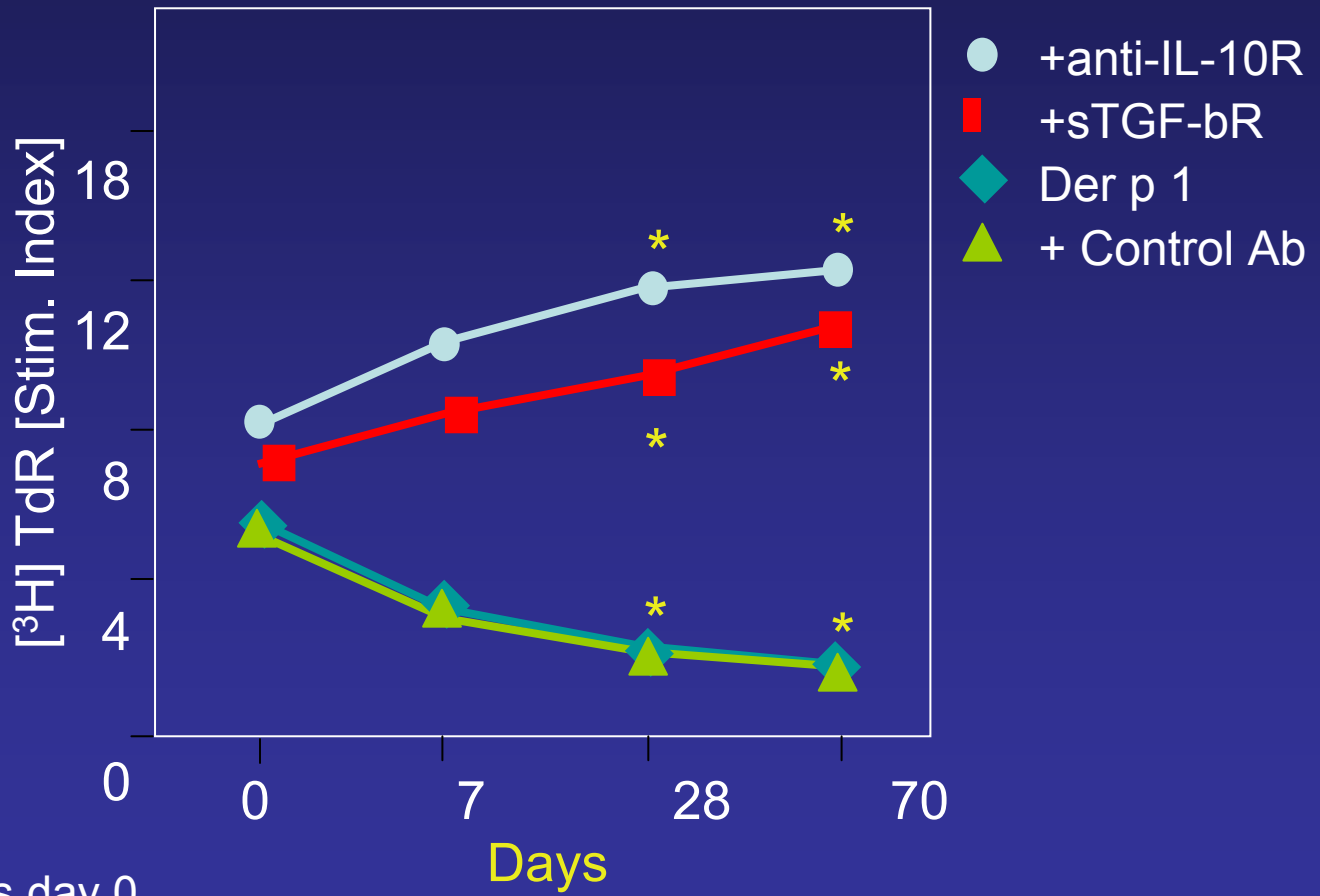
Normal Immune Response: *Downregulation of Th1 and Th2 Response by IL-10 and TGF-β*



*P < .01.
TdR = thymidine.

Jutel M et al. *Eur J Immunol*. 2003;33:1205-1214.

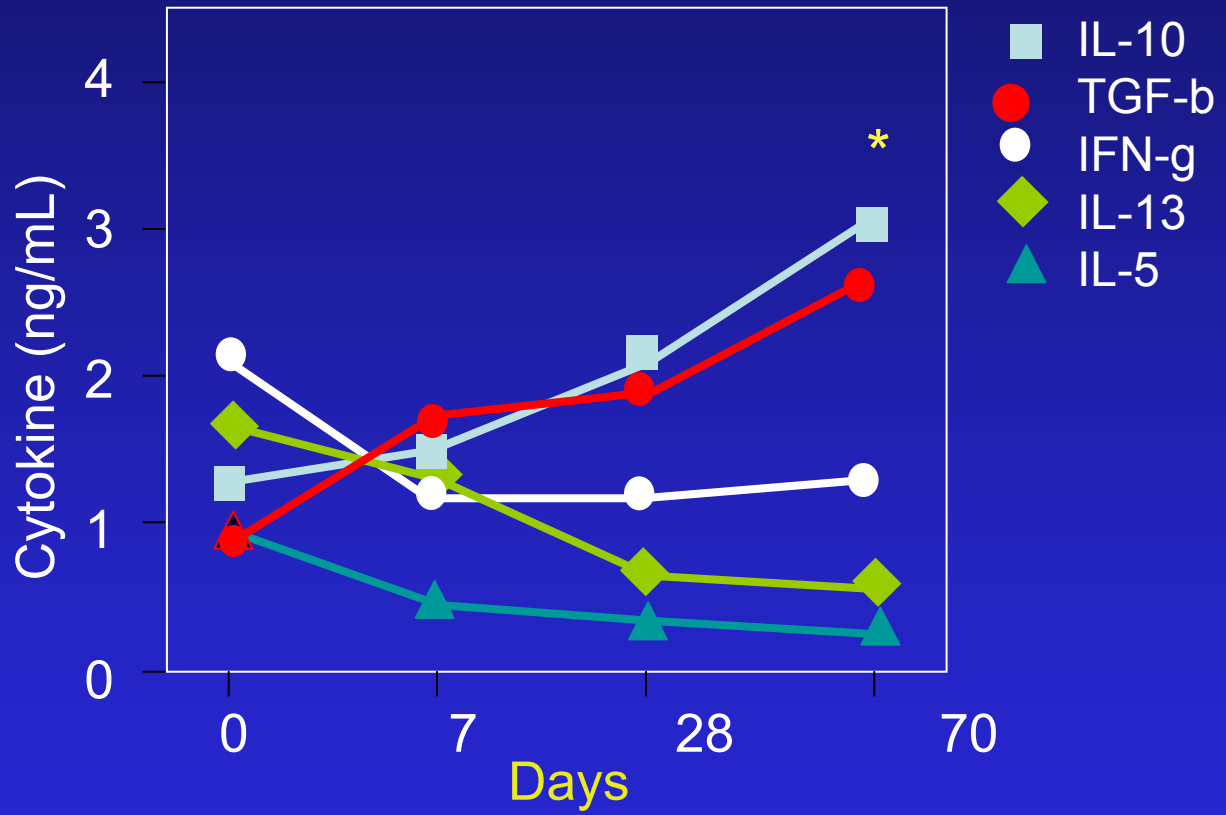
IL-10 and TGF-β Mediated T-Cell Suppression During HDM-SIT



*P < .01 versus day 0.

Jutel M et al. *Eur J Immunol*. 2003;33:1205-1214.

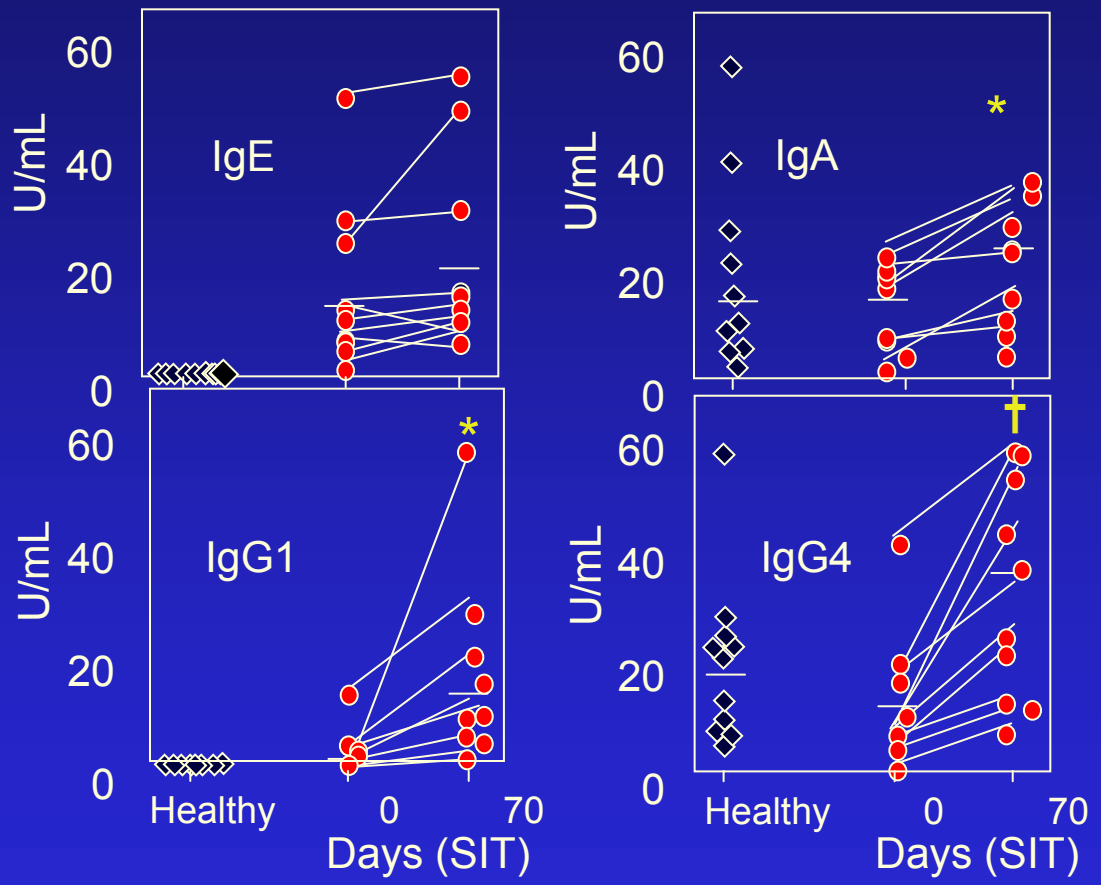
Cytokine Production During HDM-SIT



HDM-SIT = house dust mite-specific immunotherapy. *$P < .001$.

Jutel M et al. *Eur J Immunol*. 2003;33:1205-1214.

Antibody Response in Healthy Controls and Changes in Allergic Individuals During HDM-SIT



HDM-SIT = house dust mite-specific immunotherapy.
*$P < .01$. †$P < .001$.

Jutel M et al. *Eur J Immunol*. 2003;33:1205-1214.

Allergen Immunotherapy: Prevention of Progression of Diseases

- New Sensitizations in Monosensitized Subjects
- Progression to Asthma in Subjects who Only Have Allergic Rhinitis

Prevention of New Sensitizations in Asthmatic Children Monosensitized to House Dust Mite by Specific Immunotherapy. A Six-year Follow-Up Study

GB Pajno et al. Clin Exp Allergy 2001;31:1392-7

134 children, ages 5 to 8 years, with intermittent asthma with or without rhinitis, and single sensitization to house dust mite.

- Parents of 75 children accepted immunotherapy
- Parents of 63 children rejected immunotherapy.

Prevention of New Sensitizations

- Immunotherapy was administered for 3 years, with 3 years follow-up
- Maintenance dose 3.5 mcg.
- At the end of the 6 years new sensitization had occurred in:

- Immunotherapy	17/69 (24.6 %)
- Medication control	36/54 (66.7 %)

GB Pajno, et al . Clin Exp Allergy 2001;31:1392-7

Prevention of Asthma by Specific Immunotherapy (PAT)

E. Valovirta, et al. AAAAI 2006

- **Children ages 7-13 years with allergic rhinitis and no diagnosed asthma**
- **Immunotherapy for three years with Birch (13μg Bet v 1) and/or Timothy (20μg Phl p 5)**
- **Follow-up 2 and 7 years after stopping immunotherapy**

Prevention of Asthma by Specific Immunotherapy

E. Valovirta, et al. AAAAI 2006

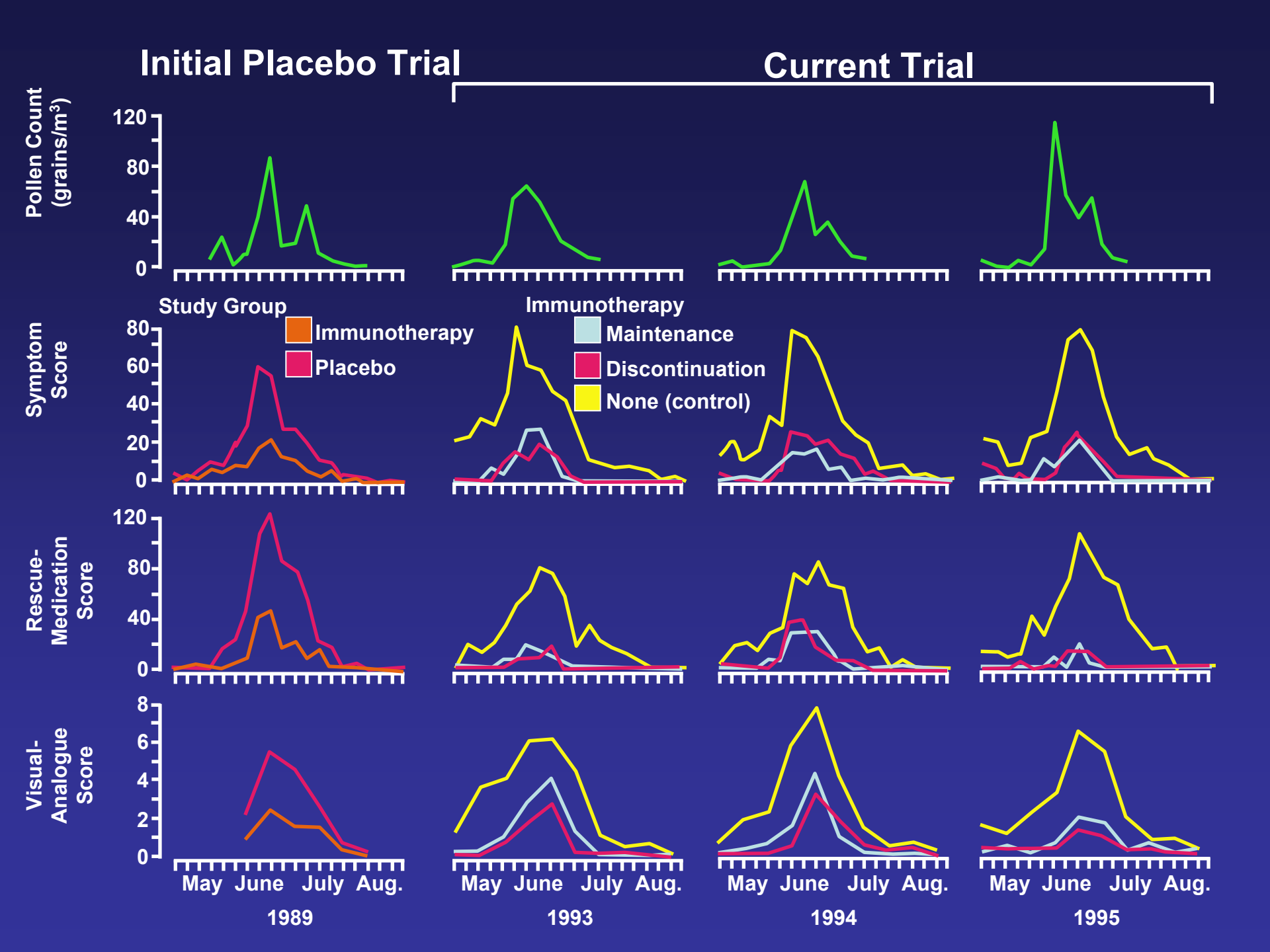
Results on follow-up: No Asthma / Asthma:

	SCIT	Control	Odds Ratio
3 years	60/19	40/32	2.52
5 years	60/15	38/29	2.68
10 years	48/16	29/24	2.48

Long-Term Clinical Efficacy of Grass-Pollen Immunotherapy

SR Durham et al. N Engl J Med 1999;341:468-75

- 32 patients received 3-4 years of grass-pollen immunotherapy
- Maintenance dose 20 μg Phl p 5
- Randomized to continue to receive monthly maintenance or placebo for 3 years
- 15 newly recruited, untreated patients of similar severity observed for natural history of disease


Initial Placebo Trial
Current Trial
Pollen Count (grains/m³)
120
80
40
0
Symptom Score
80
60
40
20
0
Study Group
Immunotherapy
Placebo
Immunotherapy
Maintenance
Discontinuation
None (control)
Rescue-Medication Score
120
80
40
0
Visual-Analogue Score
8
6
4
2
0
May June July Aug.
1989
1993
1994
1995

Alternative Approaches in Allergen Immunotherapy

Present Status of Allergen Immunotherapy

- Safety and efficacy of allergen immunotherapy is limited by reactions of the allergen extracts with specific IgE
- The clinically relevant immunologic response appears to be due to direct action on T-lymphocytes

Increased Safety with Currently Available Extracts

- **Delayed absorption:**
  - **Aluminum**
  - **Tyrosine adsorption**
  - **Encapsulation (liposomes)**
- **Reduce levels of IgE**
  - **Omalizumab**
- **Alternative route**
  - **Nasal/bronchial**
  - **Oral (microencapsulation)**
  - **Sublingual**

Omalizumab Pretreatment Decreases Acute Reactions after Rush Immunotherapy for ragweed-induced Seasonal Allergic Rhinitis

TB Casale, et al J Allergy Clin Immunol 2006;117:134-40

- 123 adults with ragweed allergic rhinitis
- Pretreated with 9 weeks of omalizumab or placebo
- 1 day rush immunotherapy to top dose of 1.2 mg Amb a 1
- Followed by 12 weeks of combined omalizumab or placebo and weekly immunotherapy with increase in dose to 12 mg Amb a 1.

Reduction of IgE by Pre-Treatment with Omalizumab: Results

- Anaphylaxis risk vs. placebo during RIT:
  - IT alone OR 12.1
  - Om plus IT OR 2.1
- Anaphylaxis risk vs. placebo during weekly build-up:
  - IT alone 9.7%
  - Om plus IT 0%

TB Casale, et al. J. Allergy Clin Imm 20061117:134-40

Present Status of Sublingual Immunotherapy (SLIT)

- Safe and convenient
- Plausible mechanism
- Demonstrated prevention of:
  a. New sensitization
  b. Progression from rhinitis to asthma
- Persistence of efficacy after stopping

But:

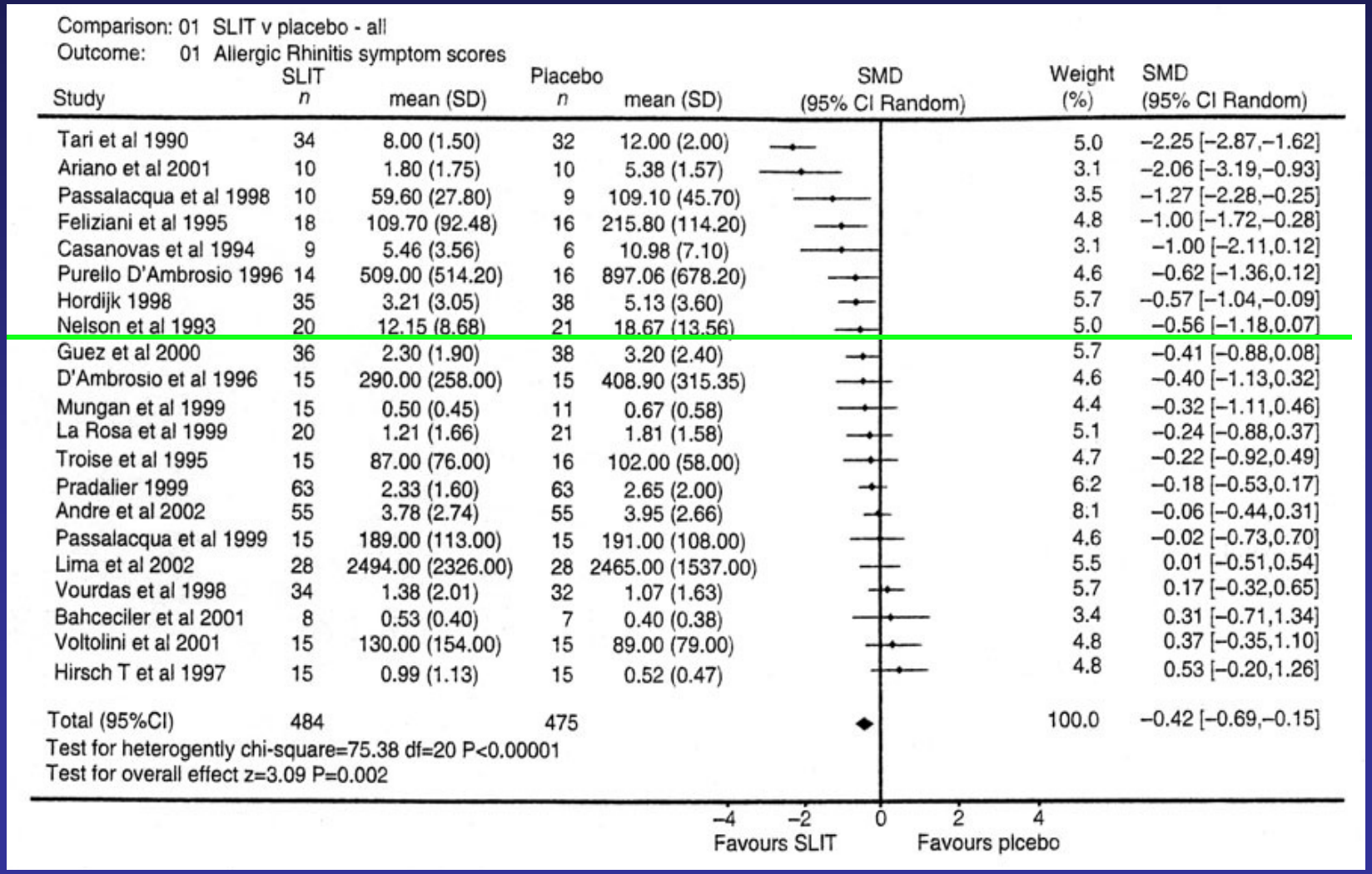
- Less effective than SCIT
- Untested for multiple allergen mixes
- In U.S. lack of approved extracts and billing code.

Sublingual Immunotherapy for allergic Rhinitis: Systematic Review and Meta-Analysis

DR Wilson, M Torres Lima, SR Durham Allergy 2005;60:4-12

- 21 trials involving 959 patients were included, all were DBPC parallel design.
- Overall standard mean reduction in
  - Symptoms - 0.42 ($p = 0.002$)
  - Medications: - 0.43 ($p = 0.00003$)
- No clear relation to allergen administered or duration.
- Insufficient data to analyze for dose.

Sublingual immunotherapy for allergic rhinitis: systematic review and meta- analysis. DR Wilson, M Torres Lima, SR Durham. Allergy 2005:60:4-12.



Comparison: 01 SLIT v placebo - all
Outcome: 01 Allergic Rhinitis symptom scores

Study	SLIT n	SLIT mean (SD)	Placebo n	Placebo mean (SD)	Weight (%)	SMD (95% CI Random)
Tari et al 1990	34	8.00 (1.50)	32	12.00 (2.00)	5.0	−2.25 [−2.87,−1.62]
Ariano et al 2001	10	1.80 (1.75)	10	5.38 (1.57)	3.1	−2.06 [−3.19,−0.93]
Passalacqua et al 1998	10	59.60 (27.80)	9	109.10 (45.70)	3.5	−1.27 [−2.28,−0.25]
Feliziani et al 1995	18	109.70 (92.48)	16	215.80 (114.20)	4.8	−1.00 [−1.72,−0.28]
Casanovas et al 1994	9	5.46 (3.56)	6	10.98 (7.10)	3.1	−1.00 [−2.11,0.12]
Purello D'Ambrosio 1996	14	509.00 (514.20)	16	897.06 (678.20)	4.6	−0.62 [−1.36,0.12]
Hordijk 1998	35	3.21 (3.05)	38	5.13 (3.60)	5.7	−0.57 [−1.04,−0.09]
Nelson et al 1993	20	12.15 (8.68)	21	18.67 (13.56)	5.0	−0.56 [−1.18,0.07]
Guez et al 2000	36	2.30 (1.90)	38	3.20 (2.40)	5.7	−0.41 [−0.88,0.08]
D'Ambrosio et al 1996	15	290.00 (258.00)	15	408.90 (315.35)	4.6	−0.40 [−1.13,0.32]
Mungan et al 1999	15	0.50 (0.45)	11	0.67 (0.58)	4.4	−0.32 [−1.11,0.46]
La Rosa et al 1999	20	1.21 (1.66)	21	1.81 (1.58)	5.1	−0.24 [−0.88,0.37]
Troise et al 1995	15	87.00 (76.00)	16	102.00 (58.00)	4.7	−0.22 [−0.92,0.49]
Pradalier 1999	63	2.33 (1.60)	63	2.65 (2.00)	6.2	−0.18 [−0.53,0.17]
Andre et al 2002	55	3.78 (2.74)	55	3.95 (2.66)	8.1	−0.06 [−0.44,0.31]
Passalacqua et al 1999	15	189.00 (113.00)	15	191.00 (108.00)	4.6	−0.02 [−0.73,0.70]
Lima et al 2002	28	2494.00 (2326.00)	28	2465.00 (1537.00)	5.5	0.01 [−0.51,0.54]
Vourdas et al 1998	34	1.38 (2.01)	32	1.07 (1.63)	5.7	0.17 [−0.32,0.65]
Bahceciler et al 2001	8	0.53 (0.40)	7	0.40 (0.38)	3.4	0.31 [−0.71,1.34]
Voltolini et al 2001	15	130.00 (154.00)	15	89.00 (79.00)	4.8	0.37 [−0.35,1.10]
Hirsch T et al 1997	15	0.99 (1.13)	15	0.52 (0.47)	4.8	0.53 [−0.20,1.26]
Total (95%CI)	484		475		100.0	−0.42 [−0.69,−0.15]

Test for heterogently chi-square=75.38 df=20 P<0.00001
Test for overall effect z=3.09 P=0.002

−4 −2 0 2 4
Favours SLIT Favours plcebo

Sublingual Immunotherapy: A Comprehensive Review

- **47 randomized studies with outcome data: 39 DBPC, remainder randomized open or double blind comparisons without placebo.**
- **Cumulative monthly dose in relation to investigators' usual SCIT dose:**
  1-5 X n = 24
  6-50 X n = 12
  > 50 X n = 11
- **All studies with single allergens**

L Cox, et al. JACI 2006

Sublingual Immunotherapy: A Comprehensive Review AAAAI/ACAAI Task Force Report

L Cox, DL Linnemann, H Nolte, D Weldon, I Finegold, HS Nelson. JACI 2006;117:1021-35

- 103 papers reviewed
- 47 randomized studies provided outcomes: 39 DBPC, 5 randomized without placebo, 2 SLIT vs. SCIT, and 1 comparing two doses.
- Cumulative monthly dose in relation to investigators' usual SCIT dose:
  1-5 X n = 24
  6-50 X n = 12
  > 50 X n = 11
- All studies with single allergens

SLIT: Treatment Related Serious Adverse Events

In 3984 patients treated with 1,019,826 doses there were 14 probable SLIT-related SAEs:

Asthma - Severe	n = 5
Asthma - Persistentnt	= 3
"Worsening allergies"	n = 2
Mild Uvula Edema	n = 1
Urticaria - 48 hours	n = 1
Abdominal Pain	n = 1
Vomiting	n = 1

No life-threatening reactions or deaths reported

L Cox, et al. JACI 2006

SLIT: Dose-Response (X SCIT)

Dose	Dur	Better Sx	Better Med	Not Better Sx	Not Better Med	2nd Year Sx	2nd Year Med
1-5 X	≤ 12	14	7		5		
	>12	6	4	3	4	1	3
6-50X	≤ 12	7	7				
	>12	3		2	3		
>50X	≤ 12	3	3	1	1		
	>12	4	1	2	5	2	
Totals		37	22	8	18	3	3

Sublingual Immunotherapy with Once-Daily Grass Allergen Tablets: A Randomized Controlled Trial in Seasonal Allergic Rhinoconjunctivitis.

SR Durham et al. J Allergy Clin Immunol 2006;117:802-9

- 855 subjects from 8 countries, 18-65 years of age with history of grass SAR, positive PST and grass-specific IgE.
- Treated daily, without build-up, with 2,500, 25,000, and 75,000 SQ units (75,000=15 mcg phl p 5).
- Mean duration of treatment 18 weeks.

Sublingual Immunotherapy with Once-Daily Grass Allergen Tablets: Results

- No differences between results with placebo and two lowest doses (2,500 & 25,000)
- For those beginning 75,000 units per protocol (≥ 8 weeks before the pollen season:
  - Symptoms reduced 21% ($p = .002$)
  - Medication reduced 29% ($p = .012$)
- Adverse events related to treatment (mainly oral pruritis or throat irritation and early in treatment) reported by 78% of high dose group.

SR Durham et al. J Allergy Clin Immunol 2006;117:802-9

Future Approaches to Allergen Immunotherapy

- **Reduce the reactivity with IgE:**
  - Disrupt IgE epitopes (usually conformational)
  - Preserve T-cell epitopes
- **Shift the immune response to allergen away from the Th2 phenotype**
  - Stimulate innate immune system

Future Approaches to Allergen Immunotherapy

- **Modification of Allergens:**
  - **Allergoids**
  - **Polymerized extracts**
  - **Allergenic peptides**
  - **Site-directed mutagensis and deletion**
- **Immune Stimulation**
  - **ISS-ODN**
  - **Lipid A**

Immunostimulatory Sequences

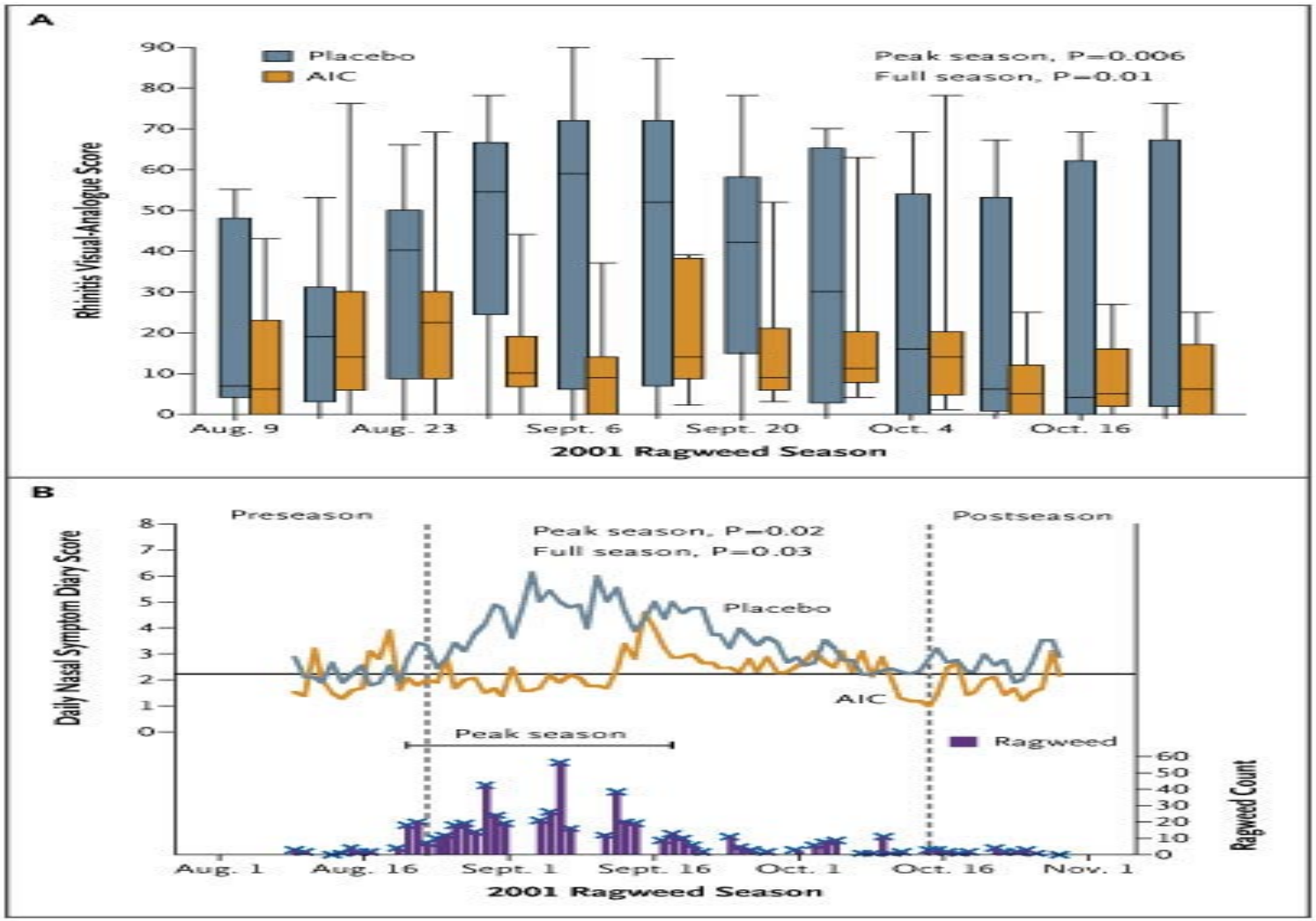
- Commonly found in bacterial and viral DNA, uncommon in vertebrates
- Commonly consist of:
  - two 5' purines
  - a CpG motif
  - two 3' pyrimidines
- Stimulate the innate immune system:
  - Macrophages: IFN-α,β IL-6, IL-12, IL-18
  - NK cells: IFN-γ
- Biases adoptive immune response towards Th1

Immunotherapy with a Ragweed-Toll-Like Receptor 9 Agonist Vaccine for Allergic rhinitis

PC Creticos et al. N Engl J Med 2006;355:1445-55

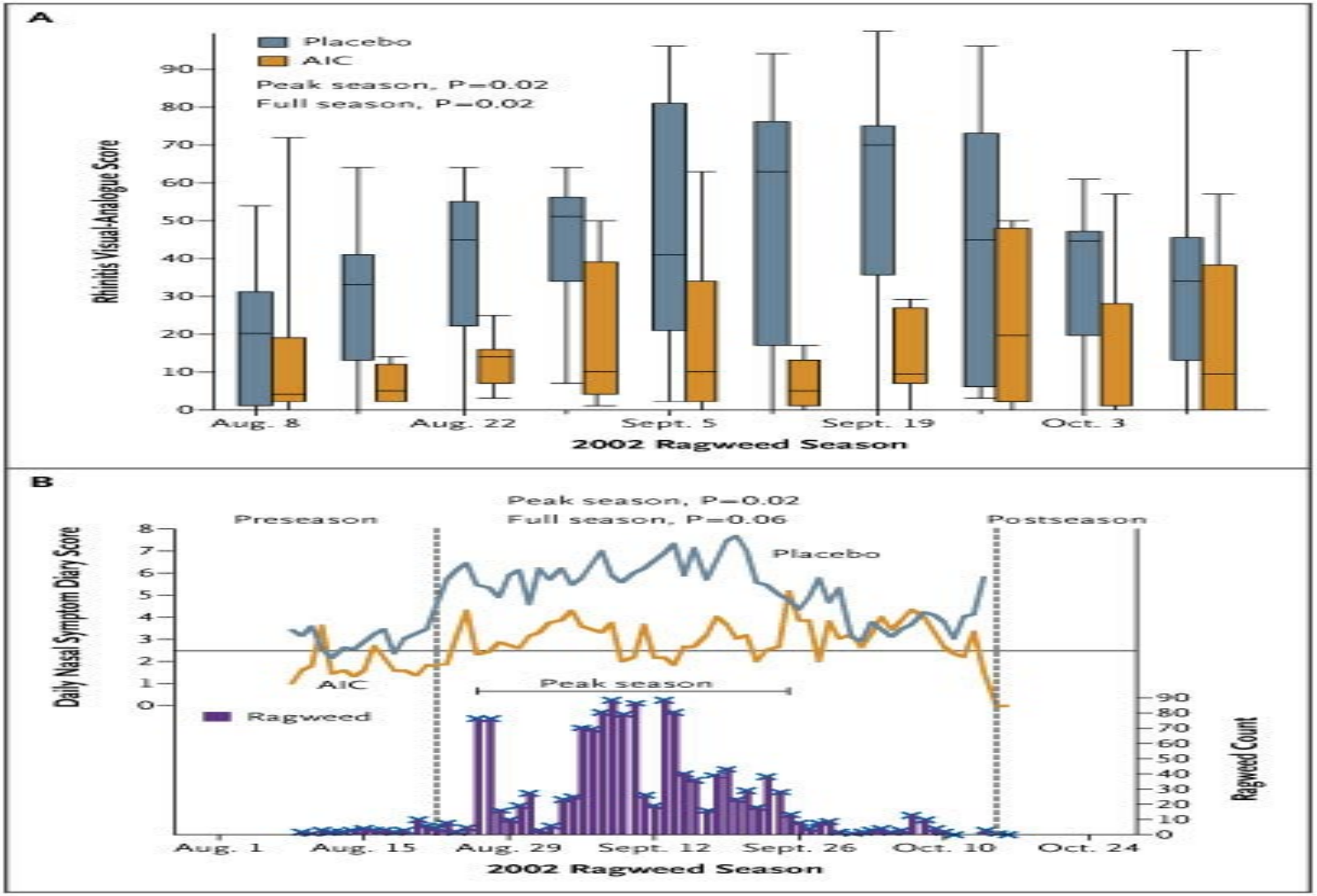
- 25 adults allergic to ragweed received immunotherapy with immunostimulatory CpG DNA sequences covalently bound to Amb a 1.
- Subjects received 6 weekly injections containing from 0.06 mcg to 12 mcg of Amb a 1.
- They were followed through two ragweed seasons without further treatment.
- 19 completed the first year and 15 the second.

Results for the First Ragweed Season



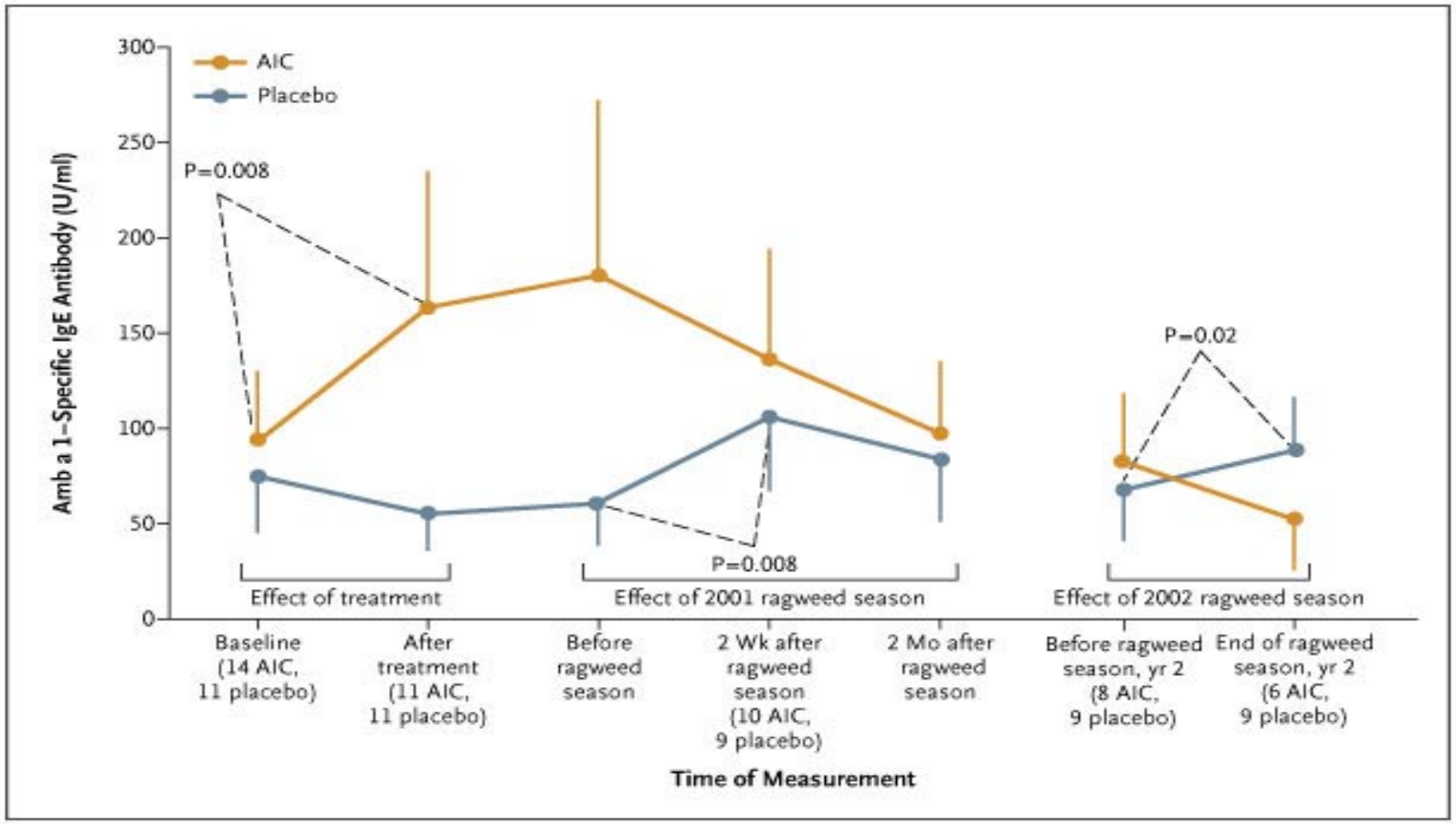
Creticos et al N Engl J Med 2006;355:1445-53

Results for the Second Ragweed Season



Creticos et al N Engl J Med 2006;355:1445-53

Effect on Amb a 1-Specific IgE



Creticos et al N Engl J Med 2006;355:1445-53